Untoward Reactions
of
Cortisone and ACTH

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Untoward Reactions of Cortisone and ACTH

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FOREWORD

In recent years the physician's armamentarium of agents to combat the course of disease has been strengthened by the addition of many drugs of unquestioned potency. Never before has the physician had access to as many valuable therapeutic preparations as are available today, but from these therapeutic triumphs there has emerged a new and challenging problem, namely, the untoward reactions that may result from poorly directed, promiscuous or prolonged use of certain therapeutic agents Some of these reactions to therapy are physiologic and desirable; others are contraphysiologic and undesirable. Some occur unexpectedly and without definite patterns, others initiate a sequence of events that may be predicted and controlled. The majority of the untoward pharmacologic responses to therapy are minor and reversible in character; however, others are progressive and serious in the ultimate consequences. In the selection of therapeutic agents, the physician must pay increasing attention to the undesired or unexpected reactions that may occur during the therapy of any disorder and in no instance is this statement more true than those untoward reactions resulting from the use of cortisone and ACTH, two of the most potent drugs available today Since these agents are relatively new and periods of observation of necessity comparatively short, our knowledge of the actions of these preparations is quite limited Drs. Derbes and Weiss warrant our commendation for recording the untoward reactions that have been observed to date from the use of these two therapeutic agents.

ROSCOE L. PULLEN, M.D.

ACKNOWLEDGMENTS

Through the courtesy of Dr. Fred W. Wittich, editor and publisher, much of this material, which was previously published in the *Quarterly Review of Allergy and Applied Immunology*, is being reprinted in an expanded form.

Miss Selma De Bakey, Medical Editor, Editorial Division, Alton Ochsner Medical Foundation, has been most helpful in getting some semblance of order in a confused subject. Any niceties of phrase or felicities of expression which it may contain are hers. We lay claim to such mistakes as are present.

Our thanks are also due to Dr. Roscoe L. Pullen, Editor of American Lectures in Internal Medicine, not alone for the preface but for his many helpful suggestions.

Final thanks are due to our publishers for expediting the publication.

V. J. D.
T. E. W.

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1
INTRODUCTION

CORTISONE and ACTH, like most medicinal preparations, have a number of effects on the human subject. The immense changes wrought by these agents in healthy or diseased persons may be quite desirable or entirely undesirable, or the majority may be beneficial and one or a few deleterious. It is not correct to categorize all these unwanted features as "side reactions" since many are normal physiologic consequences and others may be disadvantageous only in certain circumstances To illustrate the latter, the development of osteoporosis following use of these agents may lead to painful fractures in the absence of trauma; to utilize this feature Stinchfield[88] recommended placing cortisone in traumatized joints during performance of arthroplasties to prevent fibrous tissue formation.

Because there are repeated references in the literature to the common disturbances associated with use of these drugs, no effort has been made to refer to each article in which a given reaction is mentioned.

2
PHYSIOLOGY

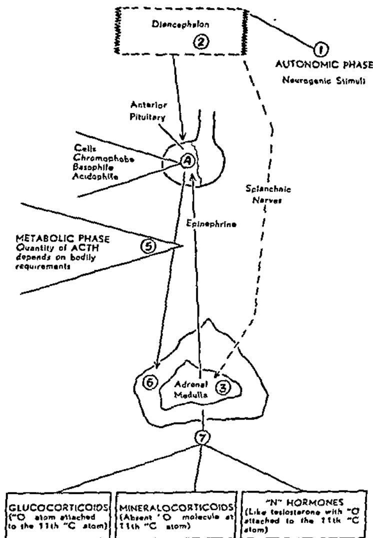
ADMINISTRATION of either ACTH or Compound E, or endogenous release of these agents in a human being, will initiate many physiologic responses. These will be briefly summarized in the following paragraphs.

The anterior pituitary gland is composed of at least three types of cells, the acidophile, the basophile and the cromophobe. Hormones are formed by the acidophiles and basophiles. One of those produced by the former is the adrenocorticotropic hormone (ACTH). At present release of ACTH from the anterior pituitary seems dependent on stimulation of the adrenal medulla with epinephrine produced, this in turn activates the anterior pituitary. This is by no means the complete explanation. McDermott and co-authors,[54] on the basis of their own observations as well as those of Ingle and associates,[43] the Sayers,[72] Cheng and Sayers,[15] and Recant and associates,[67] described a dual mechanism controlling release of ACTH. One of these, which they labelled the autonomic phase, depends on activation of the sympathetic nervous system, and the other, which they called the metabolic phase, on utilization of the adrenal cortical hormone in the body. In the normal animal under stress it seems that first the diencephalon is affected and forms a center for transmitting stimuli from an autonomic source. The adrenal medulla is then activated and the released epinephrine results in a consequent release of ACTH from the anterior pituitary. This anterior pituitary secretion seems to be controlled in that here the metabolic phase begins and the quantity of ACTH released

is dependent on the bodily requirements of the adrenal cortical steroids. The Sayers[72] believed that varying blood levels of adrenal cortical hormones furnish the necessary medium for control

Adrenocorticotropic hormone increases the outflow of the adrenal steroids and this in turn produces numerous physiologic alterations or adjustments. Whereas these closely integrated functions often tend to overlap, they can be grouped, depending on the steroid responsible, into those caused by the glucocorticoids, by the mineralocorticoids and by those corticoids exhibiting androgenic or anabolic activity ("N" hormones). The glucocorticoids are those steroids concerned with the intermediary metabolism of protein and carbohydrate. The steroids of this group are structurally related in that they all have an oxygen atom attached to the eleventh carbon atom Cortisone (Kendall's Compound E), 11-dehydrocorticosterone (Kendall's Compound A), corticosterone, and 17-hydroxycorticosterone (Kendall's Compound F) are in this group. The principal metabolic effects of these compounds are increased conversion of endogenous protein to carbohydrate (gluconeogenesis); increased conversion of exogenous carbohydrate to glycogen; rise in the blood sugar level; more mobilization and utilization of fat, with less oxidation of available carbohydrates, destruction of lymphocytes and eosinophiles as well as lymph nodes, depression of the function of the adrenal cortices as well as the thymus gland; production of negative nitrogen balance, either as a result of increased protein catabolism, decreased protein anabolism, or both; increased antihyaluronidase activity and in some manner an increase in the resistance of the organism to certain forms of stress (*e g.*, starvation, physical exertion, and exposure to cold or trauma). Cortisone and Compound F also cause moderate sodium and water retention, but to a much less degree than do the mineralocorticoids

The mineralocorticoids are those adrenal steroids having a



(Numbers 1-7 denote probable routes of stimuli)

GLUCOCORTICOIDS	MINERALOCORTICOIDS	"N" HORMONES
Cortisone (Kendall's Comp E) 11-Dehydrocorticosterone (Kendall's Comp. A) Corticosterone (Kendall's Comp B) 17-Hydroxycorticosterone (Kendall's Comp. F)	Desoxycorticosterone 11-Desoxycortisone (Reichstein's Comp. S)	Andrenosterone Estrone (?) Progesterone (?)
Actions Gluconeogenesis ↑ Exogenous CHO to Glycogen ↑ Blood sugar level ↑ Mobilization and utilization of fat ↓ Oxidation of available CHO ↓ Adrenalcortical tissue and thymus Destruction of lymphocytes and eosinophiles ↑ Protein catabolism ↓ Protein anabolism ↑ Antihyaluronidase activity ↑ Resistance of organism to certain forms of stress ↑ Na retention ↑ Urinary excretion of potassium	Actions: Urinary retention of Na & Cl ↑ Plasma volume ↑ Extracellular fluid volume ↓ Na & Cl in perspiration ↑ Urinary excretion of potassium	Actions: Retention of — Nitrogen Phosphorous Potassium Na Cl

predominant effect on electrolytic and fluid balance. Absence of an oxygen molecule at the eleventh carbon atom is characteristic of this group. Desoxycorticosterone is the most potent steroid of this type. It causes urinary retention of sodium and chloride, increased plasma and extracellular fluid volume, and decreased concentration of sodium and chloride in perspiration. The effects on water and electrolytic balance are similar to those of cortisone but approximately thirty times as great. They also produce increased urinary excretion of potassium, which is probably caused by loss of intracellular potassium due to protein breakdown, and displacement of intracellular potassium by retained sodium. The other metabolic effects, some of which are similar to cortisone and Compound F, are weak.

The third group of adrenal steroids, which are essentially sex hormones, exhibit androgenic or anabolic activity. They are related to testosterone but carry an oxygen molecule at the eleventh carbon atom. Adrenosterone is one of these steroids and possibly estrone belongs in this group. The adrenal androgens are held partially responsible for such secondary sex characteristics as growth of hair in pubic and axillary regions and on the extremities. Like testicular androgens, they cause retention of nitrogen, phosphorus, potassium and sodium chloride. Their anabolic activity, though, is weak. Whether additional steroids are secreted by the adrenal cortex is not clear, and it is possible that all adrenal cortical activity is merely the action of two or three primary hormones. It is obvious, though, that the action of ACTH or one of the adrenal steroids which it produces is extremely extensive and complex, and the exogenous introduction of these drugs will bring about many alterations in the clinical picture, which were not evident prior to their widespread therapeutic use.

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GLANDS OF INTERNAL SECRETION

Pituitary: ACTH causes increase in basophiles of anterior pituitary with Crooke's cytoplasmic changes and basophilic stippling of chromophobes. May cause focal adenomatoid accumulation of basophiles.

Adrenal: ACTH may cause hypertrophy of the cortex initially, and functional regression after withdrawal Cortisone depresses adrenal cortical activity and may cause atrophy of fascicular and reticular layers of cortex
Glucocorticoids and 17-ketosteroids increase in urine.

Pancreas: ACTH and cortisone are diabetogenic and may produce decrease in glucose tolerance, glycosuria, and decreased glutathione levels.

Thyroid. Function depressed by cortisone.

Gonads: Gonadal function depressed: Prostate, seminal vesicles, testes, ovaries decrease in size after ACTH and cortisone, libido and potentia initially increased, then decreased, cortisone may produce amenorrhea

ADMINISTRATION of ACTH or cortisone causes both structural and physiologic changes in many of the glands of internal secretion As pointed out by Albright,[2] all or almost all patients with Cushing's syndrome have certain changes in the basophilic cells described by Crooke.[20] Golden and associates,[31] who reported deaths following administration of ACTH in two patients with chronic glomerulonephritis, noted morphologic changes in the anterior pituitary that consisted of an increase in the total number of basophiles with Crooke's hyaline cyto-

plasmic changes and basophilic stippling of many of the chromophobes. They suggested that these changes reflect storage of endogenous ACTH following stimulation of the adrenal cortex by therapeutic administration of this hormone. These authors reported another observation on a patient with myasthenia gravis who had received ACTH nine and six months before death (975 and 500 mg.); the pituitary gland showed a focal increase in basophiles resembling an adenoma, the basophilic count was 13.9 per cent and only a few Crooke's changes were seen. The question was raised: does the focal adenomatoid accumulation of basophiles represent a residual effect of ACTH therapy?

Pompen[63] treated Sheehan's syndrome with 5 mg. of ACTH five times daily for six days; during the time of administration of the drug improvement was noted and the laboratory studies showed an increase in the adrenocorticotropic function. Discontinuance of the drug resulted in rapid deterioration of the patient's condition. Pompen thought that the exogenous ACTH depressed the meager supply of endogenous ACTH which was sustaining the patient and cessation of treatment meant that she had no or too little endogenous ACTH to maintain life.

With the increased usage of ACTH and cortisone, there has been growing concern over their effects on the adrenal glands Forsham and co-workers[26] reported a wide variation in the final response of the adrenal cortex in patients given ACTH for more than 48 hours. Functional regression occurred within four days following discontinuation of ACTH in dosages of 40 to 200 mg. Adrenal cortical activity returned to but did not fall below the pretreatment level. In contrast administration of 100-200 mg. of cortisone a day suppressed both adrenal cortical activity and the response to ACTH for as long as 10 days after therapy.

Administration of pituitary adrenocorticotropic hormone increases the activity of the adrenal cortices. Administration of cortisone and other adrenal hormones has the opposite effect on

adrenal cortical activity and structure. Exogenous cortisone relieves the functioning adrenal cortex of its need to supply the endogenous material and it is probable that this inactivity results in atrophy of the adrenal cortices. Ingle and associates[43] demonstrated this action in rats. In man, the presence of an active adrenal cortical adenoma will result in atrophy of the opposite adrenal gland.

Winter and co-workers[95] demonstrated pronounced atrophy of the fascicular and reticular layers of the adrenal cortex of rats following prolonged administration of cortisone. They noted that the adrenal cortex weighed 40 per cent less after administration of cortisone for ten days and about 50 per cent less after six weeks. However, these changes appeared to be reversible, for in 10 days after cortisone was discontinued the adrenal cortex appeared normal.

Proctor and Rawson[64] reported a fatal case of disseminated lupus erythematosus in which both ACTH and cortisone had been employed. Of interest here was the presence of cytolytic destruction of the adrenal cortex, with most pronounced changes in the fascicular zone and some hyperplastic changes in the glomerular zone. Whether the cortisone or the ACTH, or both, caused these changes is not known. They suggested that cortisone could have caused severe adrenal cortical atrophy producing an acute need for cortical steroids and then the sudden stimulation of the adrenal cortex by ACTH in this critically ill patient produced an overwhelming holocrine type of response resulting in acute cytolysis in the fascicular zone. These same histologic changes in the adrenal cortex were noted by O'Donnell and Fajans[60] in a patient who received only ACTH. This is in keeping with observations by Selye and Stone.[74]

Sprague and associates[81] observed four types of evidence suggestive of adrenal depression by cortisone: 1) postcortisone asthenia, 2) depression of urinary 17-ketosteroids during and after administration of cortisone, 3) diminished response to

plasmic changes and basophilic stippling of many of the chromophobes. They suggested that these changes reflect storage of endogenous ACTH following stimulation of the adrenal cortex by therapeutic administration of this hormone. These authors reported another observation on a patient with myasthenia gravis who had received ACTH nine and six months before death (975 and 500 mg.); the pituitary gland showed a focal increase in basophiles resembling an adenoma, the basophilic count was 13.9 per cent and only a few Crooke's changes were seen. The question was raised: does the focal adenomatoid accumulation of basophiles represent a residual effect of ACTH therapy?

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Administration of pituitary adrenocorticotropic hormone increases the activity of the adrenal cortices. Administration of cortisone and other adrenal hormones has the opposite effect on

thione level. This suggested only a reduction in the renal threshold and possibly signifies that the various disturbances in carbohydrate metabolism are merely different degrees of disturbed physiology. Kobernick and More[19] described pronounced vacuolization or "hydropic changes" of cells of islet and ductules of pancreas in rabbits given cortisone. These rabbits had an increase in blood sugar and glycosuria. The lipid fraction increased in a pattern similar to alloxan diabetes.[61]

Thorn and associates[91] believed that the fasting blood sugar almost always rises during either ACTH or cortisone therapy and that occasionally frank diabetes mellitus may develop. In our experience elevation of the fasting blood sugar level during cortisone therapy has been unusual and we have not seen diabetes mellitus occur. Withdrawal usually results in correction of this disturbance. It is the opinion of Conn[16] that the person who is susceptible to the diabetogenic effect of ACTH is susceptible to the same effect from cortisone

Thyroid function may be depressed by the prolonged administration of cortisone. This is demonstrable by a decreased uptake of radioactive iodine by the gland, as well as a decrease in the basal metabolic rate which was reported by Sprague[85] and a decrease in the protein bound iodine noted by Hardy and co-workers [35] Hill and associates[38] reported a delayed and often inadequate adrenal cortical response to ACTH in patients with myxedema.

Administration of ACTH and cortisone also depressed gonadal function Antopol[3] noted decrease in the size of the testis, seminal vesicles and prostate in mice receiving fifty times the human dose of cortisone, and also varying amounts of suppression of spermatogenesis with the appearance of giant cells. In female mice excessive amounts of cortisone caused what appeared to be a reduction in size of the ovaries.

Ingle,[42] however, was unable to produce regression of the testes in adult rats with moderately large doses of cortisone.

pituitary adrenocorticotropic hormone, and 4) atrophy of adrenal cortices observed at necropsy. The asthenia noted following withdrawal of cortisone appears a few days after the drug is discontinued and may last several weeks. The fall in urinary 17-ketosteroid excretion is prompt and almost uniformly seen. The eosinophilic response to ACTH is also fairly uniform and reverts to normal after cortisone is discontinued. In Sprague's report the necropsy studies of the adrenal glands of nine patients who had received cortisone showed depletion of lipoid material, especially in the fascicular zone, which was significantly narrowed, whereas the glomerular zone was well preserved.

The fact that ACTH acts chiefly on the adrenal cortex also gains support from the observation of Sonenberg and co-workers,[81] who injected ACTH labelled with I^{131} into normal male rats. They noted that the material was concentrated immediately in the adrenal cortex

From the studies on dogs by Nelson and co-workers[59] it appears that the chief adrenal steroid in the adrenal vein is a 17-hydroxycorticosterone. Administration of ACTH to dogs caused a sharp rise in the secretion of Compound F, associated at first with an increase in blood flow. No significant amounts of cortisone were found

The diabetogenic effect of ACTH has been recognized for a long time, for in 1932 Houssay and associates[40] produced permanent diabetes in a dog with injections of anterior pituitary extract. In the normal adult human being continuous administration of moderately large doses of ACTH will cause diminished glucose tolerance and glycosuria and this is associated with diminished glutathione levels. Lazarow[51] reported this reduction in glutathione in the blood of rats following administration of both ACTH and cortisone.

In a patient given ACTH during an attack of pneumonia Kass and Finland[48] noted glycosuria with abnormal fasting blood sugar, normal glucose tolerance and diminished blood gluta-

4
ELECTROLYTES

Negative potassium, nitrogen, calcium and phosphorus balance.

Positive sodium, chloride balance.

Increase in plasma bicarbonate.

Increase in urinary uric acid, uric acid-creatinine ratio, cystine, methionine, SO_4.

According to Sprague and associates[85] daily administration of 100 mg of cortisone for 12 to 30 days had little effect on calcium, sodium, chloride and potassium. However, 200 mg. doses for twelve to eighteen days caused a negative potassium balance generally with retention of sodium and chloride. Following administration of 100 mg. ACTH daily for 12 days there was an increase in plasma bicarbonate and a negative nitrogen balance Retention of sodium may lead to retention of water and in those with barely compensated hearts this may precipitate congestive heart failure. Potassium depletion may lead to a clinical syndrome characterized by muscular weakness, cardiovascular collapse, with or without electrocardiographic changes, commented on in the next section, and at times a striking amount of abdominal distention, cramps and pain. Irons and co-workers[44] pointed out that in such instances the question of an abdominal surgical emergency may be raised. In their experience the differential diagnosis has been rendered more difficult by the demonstration of leucocytosis in patients treated with ACTH and cortisone. However, the lack of localizing signs of peritoneal irritation together with a lowered serum potassium value will usually permit differentiation

Boland and Headley[9] reported increase in libido and potentia during the early part of cortisone administration in four of 18 males. They noted no instance of decreased libido and potentia, but three of five men questioned by Sprague and co-workers[85] had a significant decrease in sexual drive and potency during prolonged administration of cortisone. Sprague and associates[85] also reported development of amenorrhea following administration of cortisone in three out of about 10 women in their series who had had normal menstrual function.

there is more of a tendency for rise in blood pressure after administration of these agents. Thus, one of the patients of Hench and co-authors,[37] a woman severely ill with disseminated lupus erythematosus, improved considerably during treatment with cortisone but showed a significant rise in blood pressure; there was evidence that she had antecedent parenchymatous renal disease. Knowlton and associates[47] reported that injection of nonadrenalectomized nephritic rats with cortisone produced moderate hypertension, whereas similar treatment of adrenalectomized nephritic rats caused severe hypertension. They explained this action by suggesting that other adrenal steroids produced by the nonadrenalectomized rat may counteract the pressor effect of cortisone. That this hypertensive effect in nephritis is not constant is indicated by a study of Farnsworth,[23] who observed a decrease in previously elevated pressure after ACTH was given two patients with acute and subacute glomerulonephritis.

One of the primary physiologic actions of these agents is to cause retention of sodium, chloride and hence water. This manifests itself clinically as gain in weight (often sudden), edema, ascites, pleural effusion or even anasarca. Because ACTH stimulates production of mineral corticoids, as well as the other adrenal corticoids, it is somewhat more likely to cause this water retention This may subsequently lead to congestive heart failure in persons with damaged myocardia. Massell[56] observed that retention of fluids increased previous congestive failure or precipitated the condition in patients with acute rheumatic carditis

The direct action of cortisone on the heart has been observed in adrenal insufficiency by Somerville [80] He noted that the size of the heart as reflected by the transverse diameter determined radiographically, showed an increase in five of six cases measured, whereas in the other it remained unchanged. In no case did it increase beyond normal, although in one of the five the size of the heart was within normal limits initially.

5
CARDIOVASCULAR SYSTEM

Blood pressure not altered after cortisone or ACTH in most normotensives. Common to increase 20-40 mm./Hg. systolic, 10-30 diastolic.

Hypertensive reactions may occur, especially in nephritis and disseminated lupus.

Blood pressure may decrease in hypertensives.

Water retention (weight gain, edema, ascites, pleural effusion, anasarca) may produce congestive failure

Heart enlarges (in Addison's disease).

Electrocardiographic changes noted (progressive increase in QT intervals, inversion of T waves).

Total serum cholesterol, esterified cholesterol and phorpholifidi increase after cortisone. Causative factor in early arteriosclerosis ??

Alterations in blood clotting mechanism may cause either an increase or decrease in blood coagulation.

MOST NORMOTENSIVE patients show no change in blood pressure during treatment with cortisone or ACTH. It is not uncommon, however, to observe a slight rise (20-40 mm./Hg. systolic, 10-30 mm./Hg. diastolic) after approximately ten to fourteen days of therapy In certain of these the pressure returns to normal during treatment whereas in others the elevation persists One of our patients had a striking hypertensive reaction a few days after administration of cortisone for carcinoma of the breast with metastasis. In two hypertensive patients studied by Perera and associates[62] there was a slight reduction in the blood pressure.

In nephritis, as well as in disseminated lupus erythematosus,

well known to occur in suppressed thyroid function. Finally, Heinbecker and Pfeiffenberger[36] pointed out that in Cushing's disease there is a premature atherosclerosis.

The manifold alterations induced by cortisone and ACTH may change the blood clotting mechanism. Apropos of this is Selye's[73] statement that the alarm reaction in general decreases the clotting time. He postulated that the frequent occurrence of thrombosis following surgical procedures or other injuries may be related to humoral factors released in response to stress. Smith and co-workers[76] studied the influence of ACTH and cortisone on certain factors of blood coagulation. In general, they found no consistent change from patient to patient. A single 20 mg. dose of ACTH produced in four hours a significant increase in circulating heparin or heparin-like material, a parallel prolongation of the clotting time and the usual reduction in the circulating eosinophiles. In one patient the clotting time was reduced by 15 minutes and this was paralleled by significant changes in the prothrombin system as reflected in the pronounced shortening of the plasma diluted prothrombin times. These authors listed a number of changes: initial transient increase in protamine titers and clotting times; slight but significant lowering of clotting times during therapy and return to control level when the hormone was withdrawn; a varying increase in the level of circulating heparin or heparinlike material on therapy, which, inexplicably, continued after ACTH withdrawal; significant changes both in per cent prothrombin and diluted prothrombin times which appear inverse to the changes in protamine titers. Cosgriff, Diefenbach and Vogt[18a] also noted considerable shortening of venous coagulation time, as well as decrease in heparin retarded venous coagulation time in four of six persons studied. They were unable to explain the mechanism

Incidental observations have been made on patients treated with these agents Of 175 patients treated with ACTH by Cosgriff and co-workers thrombo-embolic phenomena occurred

Electrocardiographic changes have been commented on by various authors. Thus, Soffer and associates[79] noted that during continued treatment with cortisone or ACTH serial electrocardiographic studies showed progressive increases in the QT intervals with inversion of the T waves. During treatment one patient showed two transient episodes of auricular fibrillation. In another patient pronounced sinus bradycardia developed which lasted four to five days and then became fibrillation with complete heart block. These alterations gradually reverted to a regular sinus rhythm despite continuation of treatment.

Taylor and coauthors[89] reported development of the Wenckebach phenomenon (electrocardiographic changes: depression of ST segment, inversion of T wave and progressive AV block) in patients treated with cortical steroids. He attributed these changes to potassium loss.

The development of hypercholesterolemia in rabbits after administration of cortisone was reported by Kobernick and More[49] and confirmed by Rich and associates [70] After five days there was an increase in all lipid fractions similar in pattern to that seen in alloxan diabetes.[61] Of more interest perhaps is the study of Adlersberg and associates,[1] who observed a consistent increase in the total serum cholesterol, esterified cholesterol and phospholipids in patients given cortisone. The results were less uniform and less pronounced with ACTH; in 21 of 26 patients there was an average rise of 20 per cent in the total cholesterol with the esterified cholesterol showing a similar rise. The hypercholesteremia was three times as great if patients were given long courses of either, especially if there was a high pretreatment level. Serum phospholipids paralleled cholesterol. These authors pointed out that these hormones might convert latent into overt hypercholesteremia in patients with the familial form of the disease In the discussion of the changes produced in the endocrine system it is noted that thyroid function may be depressed by these chemicals. Sustained hypercholesteremia is

6
INFECTIONS

Criteria for diagnosis and evaluation of infections may be impaired: ACTH and cortisone antipyretic, depress eosinophiles, produce transient lymphopenia, and decrease in total white count followed by increase, albumin-globulin ratio may be changed with deviations in tests based on it (ESR, etc.).

Infections may be worsened: Poliomyelitis, tuberculosis, streptococcic infections, influenza, vaccinia, trichophyton, staphlococcic infections

Because ACTH and cortisone modify the reaction of the body to microbial invasion, Beck and co-authors[6] called attention to the lack of validity of the ordinary criteria for diagnosis and evaluation of infectious disease. An antipyretic effect of cortisone was reported in tuberculosis,[23] in pneumococcal pneumonia[24] and in subacute bacterial endocarditis.[11] The temperature was practically normal in a patient with generalized peritonitis receiving cortisone.[6] One of our patients with leukemia treated with cortisone died from cerebral hemorrhage and a totally unsuspected lobar pneumonia was found at autopsy, although the patient had had no signs or symptoms referable to pulmonary disease prior to death. Fever without infection was produced experimentally in chinchilla rabbits by Recant and co-workers,[68] who noted that cortisone had an antipyretic action which was related to the size of the dose administered. The mechanism remains unknown but they suggested both an anti-inflammatory and a central action. By contrast fever has been noted during or immediately following withdrawal of

in 11; there were two deaths due to pulmonary embolism, three instances of non-fatal pulmonary embolism (one of which was associated with bilateral deep phlebitis of the legs) one case of superficial inflammation of the saphenous vein, two definite and one probable case of phlebothrombosis of the deep veins of the leg, one case of radial artery thrombosis and one case of cardiac infarction. Perera and co-workers[62] commented on increased blood clots in the menstrual flow of a patient treated with cortisone. A patient of Massell[56] treated with ACTH for rheumatic fever died of thrombophlebitis of both internal jugular veins, which he attributed to active rheumatic fever but in our experience rheumatic fever does not cause this. It has been recommended[65] that a patient with rheumatoid arthritis be treated with cortisone again after a previous course had been followed by myocardial infarction; this opinion was probably rendered without realizing that cortisone might have caused the infarction by modification of the clotting mechanism. A pulmonary infarct developed in a patient of Ragan and associates[66] 18 days after the institution of ACTH intravenously for the treatment of lupus erythematosus disseminata, up to three days before death the patient was making excellent progress and the symptoms were controlled.

Sharnoff, Carideo and Stein[72a] reported the case of a patient with moderately advanced generalized scleroderma treated with cortisone in whom the initial response was dramatic but within ten weeks irreversible hypertension developed and she died of renal insufficiency; autopsy revealed severe vascular renal lesions of the type seen in scleroderma together with thrombotic ischemic infarctions of the kidneys. The latter resembled those noted by Shick, Baggenstoss and Polley[74a] in two patients with periarteritis who died after treatment with cortisone and ACTH; at autopsy healing of vascular lesions with obliteration of the vessel lumina and widespread infarctions were noted in both

6
INFECTIONS

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BECAUSE ACTH and cortisone modify the reaction of the body to microbial invasion, Beck and co-authors[6] called attention to the lack of validity of the ordinary criteria for diagnosis and evaluation of infectious disease. An antipyretic effect of cortisone was reported in tuberculosis,[28] in pneumococcal pneumonia[24] and in subacute bacterial endocarditis.[11] The temperature was practically normal in a patient with generalized peritonitis receiving cortisone[6] One of our patients with leukemia treated with cortisone died from cerebral hemorrhage and a totally unsuspected lobar pneumonia was found at autopsy, although the patient had had no signs or symptoms referable to pulmonary disease prior to death. Fever without infection was produced experimentally in chinchilla rabbits by Recant and co-workers,[68] who noted that cortisone had an antipyretic action which was related to the size of the dose administered. The mechanism remains unknown but they suggested both an anti-inflammatory and a central action. By contrast fever has been noted during or immediately following withdrawal of

these drugs in conditions not usually associated with elevation of temperature. Kass and Finland[16] reduced the duration and intensity of febrile response to the injection of typhoid bacilli in man by previous injection of ACTH. Febrile response of rabbits to typhoid bacilli or influenza virus was similarly reduced. The mechanism is not clear but it is apparent that in some patients the temperature will fall but there will be no alteration in the fundamental pathologic processes of the illness being treated. McCombs and co-authors[53] reported cases in which fever appeared to occur at both times. We treated a physician with rheumatoid arthritis with daily oral doses of 75 mg. of cortisone in whom a severe febrile reaction associated with stupor, severe leucocytosis, and shift to the left developed. This transient episode, which presented clinical evidence of overwhelming bacterial infection, was associated with normal reactions to laboratory tests (roentgenograms, blood cultures, etc.) except for the elevated white blood cell count.

Alteration in the white blood cell count has been among the earliest changes noted, and the eosinopenic response forms the basis of the well known Thorn test. Eosinopenia can follow use of cortisone but usually large doses are necessary. ACTH leads only to transient lymphopenia; observations by Yoffey[96] on guinea pigs suggests that following ACTH the bone marrow showed no demonstrable increase of damaged cells but a statistically significant increase in the lymphocyte control, which may be an important contributory, if not the main factor in the development of lymphopenia after administration of hormones. There is also a transient reduction in the total white blood cell count. After one or two hours the white cells increase owing to an absolute increase in polymorphonuclear cells, especially the stab forms.[6] An especially impressive instance of this was reported by Caldwell and co-authors[12] whose patient had agranulocytosis. After cortisone was administered, the white cell count was 25,400 per cu. mm. Here again the clinican may be confused.

A further source of difficulty in evaluating patients arises from change in serum protein produced by these agents. Gross changes in the albuminglobulin ratio occur in patients with rheumatoid arthritis. More refined studies using electrophoretic technics confirmed these changes.[69] With these alterations one would expect deviations in the erythrocytic sedimentation rate and such indeed have been reported. Other diagnostic procedures based on serum proteins (complement fixing antibodies, agglutinating antibodies) may be modified.

There is some evidence that deleterious results may occur when these hormones are administered to patients with infections. For the most part this evidence is of an experimental nature but some of it arises from clinical experience. The instance of poliomyelitis is interesting. Pregnant women are said to be more prone to paralytic poliomyelitis[5,27] and are prone to more severe manifestations especially during the final trimester. A study by Knox[48] using pregnant mice inoculated with murine poliomyelitis disclosed a mortality rate almost double that of the control animals. After parturition there was a rapid return of resistance to normal levels. These experiments confirmed the clinical impression but did not explain it Shwartzmann[75] reported acceleration and intensification of poliomyelitis in mice receiving cortisone. He attached greater significance to the result observed in hamsters, animals naturally refractory to poliomyelitis. In these animals a mild infection is transformed into a rapidly progressing, violent and uniformly fatal disease. Further confirmation of the relationship of these hormones to deterioration of poliomyelitis in pregnancy comes from studies of Jailer and Knowlton,[45] who noted ACTH-like activity in the placenta of a woman with Addison's disease. Venning[93] had earlier reported pronounced increase in urinary glucocorticoids and a slight rise in 17-ketosteroids in the latter months of pregnancy. This corresponds to the time in pregnancy when poliomyelitis has been noted to worsen and it parallels the time during

pregnancy when improvement of arthritis and asthma often takes place. Millikan and Eaton[58] and Coriell and associates[18] noted no alteration in the clinical course of poliomyelitis.

ACTH given in daily doses of 0.25, 0.5, 1.0 and 4.0 mg. exerted an unfavorable effect on the course of experimental airborne influenza A infections in mice.[51a] An interesting if somewhat oblique confirmation of this is offered by Kilbourne and Horsfall.[46a] They noted that the concentration of various strains in influenza A and B virus as well as one strain of mumps virus in the allantoic fluids of eggs injected with cortisone acetate was much greater than the concentration of these agents in the allantoic fluid of control eggs. There is impressive experimental evidence that tuberculosis also can be made worse by administration of these preparations. Michael, Cummings and Bloom[57] observed that in rats receiving cortisone tubercle bacilli multiplied more rapidly, produced more diffuse disease and resulted in death of an animal normally immune to this organism Similar deleterious effects were noted in mice[21] and guinea pigs.[82] Human beings usually show prompt subjective improvement but doubtful improvement or actual deterioration in the underlying disease. Reports[92] from the Veterans Administration of 13 patients with far advanced tuberculosis treated with ACTH in addition to p-aminosalicylic acid and streptomycin indicated rapid transitory clinical improvement but roentgenographic evidence of a greater tendency to cavitation. As suggested in an editorial[22] in *Lancet*, until more information is forthcoming the wise course will be to regard cortisone and ACTH as liable to do more harm than good to tuberculous processes and to give them to tuberculous patients only for pressing other indications. Moreover, an unrecognized or even unrecognizable tuberculous focus may be exacerbated or activated by a course of these drugs given for approved reasons. Certainly when prolonged courses of these agents are to be given frequent roentgenograms of the chest are indicated

Other bacteria may flourish under the influence of these agents. Antopol[3] observed granulomatous lesions in mice treated with cortisone; corynebacterium pseudotuberculosis murium were cultured from these lesions. Thomas and Mogabgab[90] reported considerable increase in severity of infection due to streptococcus hemolyticus in the tissues and blood of rabbits following injection of cortisone. They also noted that cutaneous hemorrhagic lesions could be produced by intradermal meningococcic toxin in rabbits following treatment with ACTH or cortisone. This type of cutaneous damage was not seen in untreated animals. In a patient of Perera and co-workers[62] in whom there was no systemic reaction a hemolytic streptococcus aureus abscess developed on the left breast, which spread quickly and showed rapid sloughing and failure to heal with abundant thick purulent material No epithelial or granulation tissues appeared in spite of administration of penicillin and bacitracin. However, six days after administration of cortisone was discontinued, the lesion began to heal normally. In the patient of Beck and associates[6] there developed during treatment with ACTH acute generalized peritonitis with a heavy growth of pneumococci but the temperature and pulse rate were practically normal and muscular resistance was not increased

Kligman and co-workers[46b] found that cortisone exerted an adverse effect on the course of infections experimentally induced in guinea pigs with trichophyton mentagrophytes, vaccinia virus and Staphylococcus aureus. In most instances, especially of reinfection, the damage to the host was accentuated and the lesions were of a more severe character Smadel and co-authors[75a] reported the occurrence of relapse in two of eight patients with typhoid fever treated with cortisone and chloramphenicol, which represented a higher incidence than would ordinarily be expected in patients who received a full two weeks' course of chloramphenicol; they did not know whether this was a mere coincidence or was related to supplementary use of cortisone.

Local reaction to cortisone may not differ from that of any other agents that can be administered intramuscularly. A gluteal abscess requiring incision and drainage developed during the course of intramuscular injections of cortisone in a patient of ours with rheumatoid arthritis. An abscess (sterile) due to a liver injection was incised and drained at the same time as the gluteal abscess and it was believed that both abscesses reacted and healed in about the same time. It is important to note that the abscess due to cortisone was sterile; the patient received no more Compound E after the abscess developed.

7

MUSCULOSKELETAL SYSTEM

Muscular weakness and exhaustion may follow.

Growth may cease after cortisone (mice).

Osteoporosis and spontaneous fractures (human) due to negative calcium and potassium balance.

Fracture healing delayed (rabbits).

Cleft palate produced (mice).

MUSCULAR weakness and exhaustion were observed in four of 15 patients treated with cortisone by Boland and Headley.[9] Sprague and associates[84, 85] also reported the development of this symptom during prolonged courses of cortisone, during shorter courses of ACTH and following a course of either. Its cause is unknown but it is perhaps due to low serum and plasma potassium values. Muscular development, in fact total growth, ceased when cortisone was administered to mice by Winter and associates.[95] According to Landauer,[50a] adrenal cortical extract injected into eggs either before the beginning of incubation or at 120 hours of development delayed growth of chicken embryos considerably but did not cause malformations. Cortisone was shown to have this same embryo-stunting effect.[45a] According to Morris,[58a] ACTH inhibits the action of the pituitary growth hormone which regulates the rate of protein synthesis in the organism with a consequent increase in the amount of amino acids in the blood and an increased excretion of nitrogen. Germuth and co-workers[29] observed numerous small areas of necrotic fibers surrounded by mononuclears and occasional giant

cells in sections of skeletal muscle of rabbits treated with cortisone or ACTH.

Osteoporosis is known to be a concomitant of Cushing's syndrome and it is not surprising to learn that there is a significant increase in urinary calcium and phosphorus during administration of ACTH and cortisone. Metabolic studies performed by Soffer and associates[78] revealed that in patients with Cushing's syndrome and virilism with a constant intake of 773 mg. calcium the total combined daily excretion of calcium in the urine and feces was 859 mg. with a negative balance of 86 mg. During administration of ACTH the negative balance increased to 1503 mg. in 24 hours; almost all the calcium excretion occurred in the stool. The total excretion thus considerably exceeded the intake. Boland and Headley[9] reported spontaneous fractures in two elderly persons, both of whom had osteoporosis before cortisone was administered. One of them had a fracture of the neck of the femur without an antecedent accident; at operation osteoporosis at the fracture site was extreme. In the second patient severe lower back pain developed without trauma; roentgenogram revealed a compression fracture of the body of the twelfth thoracic vertebra. Blunt and co-workers[8] showed that cortisone delays healing of the fractures in rabbits. In addition to prolonged delay of gross healing of the fracture and absorption of the hematoma, the connective tissue failed to regenerate. Near the end of the treatment with ACTH in one of Riley's[70a] patients with a nephrotic syndrome generalized tremors associated with hypokalemia (2.8 mEq./l) developed. Baxter and Frazer[5a] administered cortisone to pregnant mice and cleft palate appeared in 44 per cent of the offspring. The stage at which cortisone was given corresponded to the time of closure of the naso-maxillary fissure. The mechanism is unexplained.

8

CHANGES IN SKIN, SUBCUTANEOUS TISSUES AND MUCOUS MEMBRANES

Hirsutism.

Increased loss scalp hair.

Acne vulgaris.

Reddish or purplish striae.

Thinning of skin

Keratosis pilaris.

Diffuse brown pigmentation face, arms, legs, mucous membranes, palmar creases, scars, moles.

Purpura and hemorrhagic tendencies following slight trauma to skin.

Urticaria and painful nodules.

Retardation wound healing (?).

THE CUTANEOUS changes seen after cortisone and ACTH therapy may resemble closely those seen in Cushing's syndrome. Hirsutism may involve the face, upper arms and back. This generally is mild and results from prolonged therapy Hench and associates[37] reported slight increase in growth of hair in normal locations in four men Major increase in loss of scalp hair was reported by Perera and co-workers,[62] a condition known to occur in adults suffering from Cushing's syndrome. Winter and co-workers[95] noted that cortisone completely suppressed regrowth of hair in mice in an area denuded by plucking One of our patients observed the effective dose of cortisone administered for rheumatoid arthritis could be regulated by the state of his dand-

ruff. When he received an adequate dose of cortisone, his dandruff disappeared. Acne vulgaris of the face and upper thorax either appears after protracted therapy or, if present, worsens. Reddish or purplish cutaneous striae, over the abdomen, thighs, shoulders and sometimes medial surface of the axillae and breasts, may develop after prolonged treatment. Width and color of these depend on the duration and intensity of therapy; following discontinuation of use of the drug the color may fade so that they eventually resemble striae distensae. Thinning of the skin has also been reported. Castor and Baker[14] observed that the prolonged percutaneous application of adrenocortical hormones modified the histology of the skin, the changes induced being limited to the area of treatment. The epidermis became thinner and in males the size of the epidermal cells was reduced. Hair stopped growing and sebaceous glands became smaller. The thickness of the dermis was reduced; they thought this was probably due to loss of substance from the collagenous fibers, the elastic fibers remaining numerous. After 160 days of applications, the skin became refractory to the action of adrenal steroids.

Keratosis pilaris, which is a common cutaneous manifestation of Cushing's syndrome, has been reported after use of these drugs by Sprague and associates.[85] Soffer and co-authors[79] reported development of a diffuse brownish pigmentation of the face, arms and legs after two to three months of treatment with both ACTH and cortisone. He also noticed pigmentation of the mucous membranes, palmar creases, and scars. Taylor and associates[89] observed greatly increased pigmentation of the skin and darkening of moles One of his patients with melanoma had no melanotic infiltration before treatment with ACTH in an abdominal scar. One of our patients treated with ACTH became intensely pigmented to the point of diffuse melanosis. Videbaek and associates[91] noted numerous pigmented spots on the backs of the hands and forearms 10 days after ACTH treatment for rheumatic fever was discontinued. Sprague and associates[85]

found one preparation of ACTH contained appreciable melanophore hormone (intermedin) on bioassay. However, swarthy skin is characteristic of Cushing's syndrome. Many authors have commented on the moon facies and buffalo distribution of fat. Boland and Headley[9] stressed the increase in pelvic girth commensurate with gain in body weight in three women. Irons and co-workers[44] observed a tendency to constant cold perspiration in patients treated with cortisone for a long time; this bore little apparent relationship to any other factors.

Kuzell and Schaffarzick[50] reported development of a large subcutaneous hemorrhage in the arm of a patient receiving cortisone who was carrying a suitcase. The only unusual finding was a prothrombin activity of 50 per cent of normal. Purpuric lesions have been noted also by Boland and Headley.[9] Hemorrhagic diathesis which could be relieved by administration of ascorbic acid was described by Stefanini and Rosenthal[86], hemorrhagic tendencies followed minimal trauma to the skin. Cameron[13] reported ecchymoses at the site of needle punctures and severe epistaxis controlled by cauterization five days after administration of cortisone. Menkin[56a] observed that cortisone produced a rapid increase in capillary permeability. The gross picture displays fairly large sediments of the material at the site of the injection whereas the microscopic picture reveals numerous congested vessels in the treated area. This appearance, in Menkin's opinion, is probably referable to the prompt seepage of plasma with induced increase in capillary permeability. Menkin found that ACTH failed to have a similar local effect. Urticaria and painful nodules have been reported after ACTH therapy by McCombs and associates,[53] and Copeman and coauthors[17] observed development of urticaria after cortisone therapy. Howes and associates[41] reported retardation of wound healing by cortisone and Creditor and associates[19] made the same observation after use of ACTH Behrman and Goodman[7] observed complete flattening and softening of large keloidal

scars in a patient being treated with ACTH; the site of biopsy in this person had failed to heal but two to four days after cessation of treatment granulation tissue appeared and healing occurred. On the other hand, healing occurred promptly in a patient being treated with ACTH who was subjected to operation.[31] An interesting side light on the possible mode of action of prevention of healing by these hormones is suggested by Green,[32] who noted that following administration of ACTH in mice mitosis of the skin is depressed for several hours.

9
CENTRAL NERVOUS SYSTEM

Symptoms may be produced: Euphoria, self-confidence, optimism, [illegible] episodes.

Electro-encephalographic changes may follow.

Coma and *convulsions* have been reported.

Pre-existing psychologic conflicts may worsen even perhaps to frank *psychoses.*

Status epilepticus

ONE OF the earliest studies on the influence of ACTH and cortisone on the psyche was that of Rome and Braceland,[71] who pointed out that the relief of painful disabling chronic disease by cortisone would appropriately be followed by a sense of euphoria, self-confidence, optimism, acceleration in tempo of thinking and physical activity. In numerous instances this is proportionate to the relief experienced and is of short duration There is evidence to the effect that cortisone has a heightening influence on affect, aside from the relief of pain and the like For example, in Simmond's disease Forsham and associates[26] reported restoration of a dull, virtually vegetative person to her former active life, and Forsham, Thorn and Browne[25] noted considerable improvement in mood effected by cortisone in Addison's disease. Patients with Addison's or Simmonds' disease may exhibit changes of a depressive nature; they are often apathetic, negative and querulous.

Rome and Braceland[71] described a group of patients who had had some serious psychologic conflict before cortisone or ACTH was administered. This was a heterogeneous group but some showed pronounced anxiety, physical tension, hyperkinesias, phobic and other ruminative preoccupations and narcissism. These conflicts fulminated after cortisone or ACTH therapy. The cyclothymic patient experienced mild hypomania, mild depression, or both. Phobias and ritualistic behavior developed in obsessional patients. One group of four patients had exceptional reactions. In the first of these a catatonic stupor developed after being given 1.3 Gm. of cortisone followed by severe increasing catatonic excitement requiring electric shock therapy A second had a severe short acute paranoid schizophrenic reaction, which cleared ten days after use of cortisone was discontinued. A third had a brief schizoid regression and finally, one had a paranoidal panic following administration of 2.4 Gm. of ACTH with prompt return to the former schizoid pretreatment level after withdrawal of ACTH Rome and Braceland[71] believed that psychologic adaptation is disrupted by the sudden and profound alteration in the milieu interieur (by cortisone or ACTH), a stress as taxing as external environmental stress.

Mental changes of varying degree are frequent. In 26 patients treated with cortical steroids Taylor and associates[83] observed euphoria in 22, hypomania in three and frank schizoid reactions in two. Most of their patients were restless and unable to sleep or concentrate but a few became extremely alert. Depressed states frequently followed these reactions and two patients even became suicidal In none, however, did the personality change persist over three weeks after withdrawal. In a series of patients with disseminated lupus erythematosus treated with cortisone by Brunsting and associates[10] signs of cerebral stimulation and psychologic aberration, such as euphoria, garrulousness, uncontrolled giggling, bulimia, excitement, apprehensiveness, phobias and anxieties, were common. In one patient with pre-

vious psychic disturbances cortisone produced a severe anxiety neurosis with compulsive trends and guilt obsessions, but after weeks there was a gradual return to normal. Stickney and associates[87] reported the case of a patient with leukemia, aged four years, who lapsed into coma and died after satisfactory clinical and morphologic response.

Hoefer and Glaser[39] studied 15 patients who received ACTH from the standpoint of electroencephalographic and neuropsychiatric modifications. Prior to treatment seven had normal electroencephalograms, one had one normal and one slightly slow tracing and seven had basically a slightly slow rhythm. The electroencephalogram of two patients remained unaltered; 13 changed three to five days after treatment was initiated. Hoefer and Glaser[39] classed these variations as: 1. a decrease in the amplitude, regularity and continuity of the basic alpha activity and a slowing of alpha activity; and 2. appearance of large amounts of slow activity. One patient exhibited spike activity. Changes increased during treatment and returned to normal one week following therapy in most instances. These alterations apparently were unrelated to dosage or to changes in blood sugar and electrolytes. One woman, aged 35 years, became stuporous and had urinary incontinence for four days. In another woman, with rheumatoid arthritis, aged 42 years, after three days euphoria appeared, followed by increasing tension, irritability, insomnia and pressure of speech. Psychomotor activity became severe and a fully developed manic psychotic reaction occurred. Two electroencephalograms showed pronounced disorganization of alpha activity, slow waves and interspersed rapid activity. For 10 days following withdrawal of ACTH, mental symptoms persisted unchanged A state of exhaustion developed Following electric shock therapy the manic reaction cleared. Prior to her illness she had shown lability and a highly active outgoing personality. During the illness she became bitter, resentful and depressed. Hoefer and Glaser[39] considered as

possible contributing factors: alterations of dextrose metabolism interference with acetylcholine cycle, water retention, disturbances of potassium, alkalosis, toxicity and hypertension. Although they thought alkalosis might be important, they were unable to explain the electroencephalographic changes. Mental confusion closely simulating alcoholic intoxication developed in one patient with cerebral arteriosclerosis treated with ACTH by Margolis and Caplan.[55]

Convulsions have been observed by Baehr and Soffer[4] in patients with lupus erythematosus treated with ACTH; this disease, of course, is known to be associated with convulsions at times. Edema of the brain with multiple small hemorrhages was discovered at necropsy in a girl who died following treatment with cortisone for disseminated lupus.[71a] Lowell and associates[52] treated a patient with bronchial asthma with cortisone for eleven days. The patient became unconscious and had urinary and fecal incontinence but on examination all reflexes were present and there were no localizing neurologic signs. Two hours later he complained of severe headache; he lay down and had a seizure, which began with deviation of both eyes to the right followed by clonic movements of the arms and legs with recovery in two minutes. Results of spinal puncture were normal. Other causes of seizure were excluded. An electrocephalogram taken four days later was not clearly abnormal but showed an increase of slow wave activity

Irons and co-workers[41] also noted effects on the higher nervous centers but they pointed out that certain of these are in no way detrimental to therapy. Thus, all their patients felt an increased sense of well being during treatment with both cortisone and ACTH. They considered of serious import, however, with relation to continued pituitary adrenocorticotrophic hormone therapy, episodes of severe depression, hypomania or frank schizoid psychoses, which were encountered in five of 13 patients. In their experience such episodes were observed only

with ACTH therapy and constitute an immediate indication for discontinuation of use of this drug. Subsequent cortisone therapy was successfully used without recurrence of the psychoses. They described a patient whose delusional ravings bore a clear relation to previously inexpressible hostilities in a difficult familial situation. In the first week of regression of panic and better contact with reality on withdrawal of ACTH the patient expressed directly and indirectly to the doctor great fear of the revealing character of the discussion which had taken place during the panic. From the second to the fourth week during which time the patient's usual adjustments to daily life had returned, complete obliteration of memory for the episode had ensued. Irons commented that the sequence of events in this patient serves to illustrate the length of time occasionally required for subsidence of the psychologic manifestations following ACTH withdrawal

Status epilepticus with subsequent evidence of temporary or permanent damage to the central nervous system developed in three of 40 children treated with ACTH by Dorfman and his associates [21a] The prolonged convulsive episode appeared in patients with different clinical syndromes, at widely varying times in the course of therapy and while relatively small doses were being used. In none of the patients was there a serious disturbance of electrolytes.

10

GASTRO-INTESTINAL TRACT

Acute perforation of duodenal ulcers and Meckel's diverticulum after ACTH.

Mild nausea after oral cortisone.

Diarrhea after cortisone (rabbits).

SELYE[73] pointed out that the importance of the stress factor in the pathogenesis of the chronic types of gastroduodenal ulcers has been emphasized repeatedly but this is even more obvious in the acute gastro-intestinal erosions, such as "Curling's ulcer" or the "air raid ulcers." He cited Firket and Betz, who concluded concerning the acute type that "such ulcerations can complicate very diverse pathologic states in patients, especially: subacute or chronic infections, burns, surgical interventions, more or less sudden endocranial processes, intense emotional shock, anaphylactic shock, etc., all conditions which are particularly effective in eliciting an alarm reaction " In face of this it could be anticipated that ulcerations might follow ACTH therapy and such is the case. Habif and associates[33] reported a case of acute perforation of a duodenal ulcer nine hours after cessation of a 29 day course of ACTH. There were no ulcer symptoms prior to treatment. The patient appeared well except for moderately severe pain not requiring analgesics and boardlike rigidity of the abdominal wall. The perforation healed rapidly. Beck and associates[8] also recorded a case of a perforated duodenal ulcer during ACTH administration. Smyth[77] reported activation of two peptic ulcers — one of which perforated — in patients treated with ACTH. Thorn and associates[91] are of the opinion that "Although

definitive studies have not yet been completed, the clinical impression seems to have been gained that ACTH administration may aggravate the symptoms of peptic ulcer." The patient of Hanlon[34] had a perforated Meckel's diverticulum during ACTH therapy.

An interesting observation of Spiro and associates[83] may cast some light on this problem. Uropepsin is a proteolytic enzyme originating in the stomach and known to be present in the urine of healthy persons in amounts quantitatively constant from day to day and unaffected by volume, pH or specific gravity of the urine. Spiro and co-workers[83] observed that ACTH was able to stimulate uropepsin excretion to levels sometimes observed in patients with active peptic ulcers, but they stated that there is no evidence as yet that this mechanism plays any role in the pathogenesis of this disease.

One of our patients complained of nausea after oral administration of cortisone. Two patients of Heller and co-workers[36a] complained of dyspepsia after taking cortisone.

The presence of diarrhea in a large number of rabbits treated with cortisone was reported by Germuth and Ottinger.[30]

11
TREATMENT

THE INCIDENCE of untoward reactions of ACTH and cortisone therapy is difficult to estimate largely because of uncertainty as to the scope of the term. Hench and associates[37] considered such side effects as euphoria and rapid mood swings as common and of no importance Their earlier incidence of 25 per cent "significant" side effects was reduced to eight per cent later mainly because lower maintenance dosages were employed.

Careful selection of patients and close attention to details can be expected to minimize most reactions except in patients who require excessively large doses of these drugs over prolonged periods to control the disease. Since most of, if not all, the psychotic reactions have been in persons with profound personality defects prior to treatment, use of these agents should probably be discouraged in patients with a history of psychotic episodes or those with pronounced instability. Again, care should be exercised in treatment of patients with nephritis or diabetes and older women with some tendency to masculinity. According to Thorn and associates,[91] patients in whom diabetes develops under the influence of ACTH and cortisone may continue treatment, if necessary, provided adequate amounts of insulin are administered. Extreme care should also be taken in administration of these agents to persons suspected of having tuberculosis, and these preparations should not be given to those known to have this disease. Frequent roentgenograms of the chest will help preclude errors. Present state of knowledge suggests circumspection in patients with other infections. It has been sugge-

sted that antibiotics be employed simultaneously with ACTH and cortisone.

Cosgriff, Diefenbach and Vogt[18a] pointed out that ACTH and cortisone can produce a "prethrombotic" state, especially in patients in whom there are other factors which predispose to intravenous thrombosis (bed rest, infection, postoperative and postpartum states, malignancy, cardiac failure). Under such circumstances, it may prove desirable to give anticoagulants prophylactically especially if treatment with cortisone and ACTH must be continued. However, according to Cosgriff and associates,[18a] patients receiving cortisone and ACTH may be unusually sensitive to dicumarol, so that they will require significantly lower doses of dicumarol to produce an anticoagulant effect.

Water retention and edema at times disappear with continuing therapy but it is considered wise to restrict sodium from the beginning of treatment. Salt substitutes (diasol, potassium salts, ammonium or calcium chloride, neocurtasal, or cosalt) may be used. If water retention does occur, mercurial diuretics may be helpful In a recent review of ion exchange resins Sacks[71b] called attention to the fact that successful use of a cation exchange resin to achieve a negative sodium balance would represent a distinct therapeutic advance. These resins are now available for clinical use and are claimed to be of value in maintaining negative sodium balance without danger of calcium or potassium depletion when heart failure is actual or impending and digitalization is indicated.

The potassium deficiency syndrome can be prevented by daily administration of chloride or sodium bicarbonate. Once the syndrome has developed, it is best treated initially by intravenous administration of potassium followed by oral supplements as soon as feasible.

In all patients treated with ACTH and cortisone the diet should contain large amounts of protein and potassium. If

nitrogen loss is not overcome by such a diet, 25 mg. of testosterone daily may be helpful.

According to Hench and associates,[37] rounding of the face, acne, hypertrichosis, and "buffalo hump" can be controlled by administration of 10 mg. of estrogen weekly. Various schemes have been recommended, such as use of ACTH following cortisone, short interrupted courses of either, or cortisone plus insulin or gold. To date none of these has been outstandingly successful.

REFERENCES

1. [illegible]

2. [illegible]

3. Antopol, W.: Anatomic changes produced in mice treated with excessive doses of cortisone. *Proc. Soc. Exper Biol. & Med*, *73* 262-265, 1950.
4. Baehr, G. and Soffer, L. J Treatment of disseminated lupus erythematosus with cortisone and adrenocorticotropin. *Bull New York Acad. Med*, *26*:229-234, 1950
5. Baker, M E. and Baker, I. G · Acute poliomyelitis in pregnancy, report of 30 cases *Minnesota Med.*, *30*·729-734, 1947

5a. Baxter, H and Frazer, F C.: The production of congenital defects in the offspring of female mice treated with cortisone. *McGill M. J*, *19* 245-249, 1950
6. Beck, J C, Browne, J S L.; Johnson, L. G, Kennedy, B J., and MacKenzie, D W Occurrence of peritonitis during ACTH administration *Canad M A J*, *62*:423-426, 1950.
7. Behrman, H T. and Goodman, J J. Skin complications of cortisone and ACTH therapy. *J A M A*, *144* 218-221, 1950.
8. Blunt, J W., Jr., Plotz, C M, Lattes, R., Howes, E L., Meyer, K., and Ragan, C Effect of cortisone on experimental fractures in the rabbit *Proc. Soc Exper. Biol & Med*, *73*· 678-681, 1950.
9. Boland, E. W. and Headley, N E Management of rheumatoid arthritis with smaller (maintenance) doses of cortisone acetate. *J A M A*, *144* 365-372, 1950.
10. Brunsting, L [illegible] ects of *cortisone* [illegible] *Proc.* *Staff Meet* [illegible]

11. Bunim, J. J.; McEwen, C.; Baldwin, J. W.; and Kuttner, A. G.: *Proc. Am. Heart A., Sc. Session*, June 22, 1950, San Francisco.
12. Caldwell, A. L ; Adams, J. W.; Anderson, J. F. C.; and Dick, A A.· Agranulocytosis treated with cortisone. *Canad. M. A. J.* *62*:506-507, 1950
13. Cameron, D. G.· Acute leukaemia treated with cortisone. *Canad. M. A. J.*, *62*·503-504, 1950.
14. Castor, C. W. and Baker, B. L.: The local action of adrenocortical steroids on epidermis and connective tissue of the skin. *Endocrinology*, *47*:234, 1950.
15. Cheng, C. P. and Sayers, G.· Insulin hypersensitivity following the administration of desoxycorticosterone acetate. *Endocrinology*, *44*.400-408, 1949.
16. Conn, J. W.: ACTH diabetes in man; the endorgan response versus the adrenocortical response. *J. Clin. Endocrinol.*, *10*: 825, 1950.
17. Copeman, W. S. C., Savage, O.; Bishop. P. M F.; Dodds, E. C.; Gottlieb, B., Glyn, J. H. H.; Henly, A. A.; and Kellie, A. E.: A Study of cortisone and other steroids in rheumatoid arthritis *Brit. M. J.*, *2* 849-855, 1950.
18. Cornell, L. D. et al.: Use of ACTH in poliomyelitis. *Proc. First Clinical ACTH Conference*, edited by J. R. Mote, Philadelphia, The Blakiston Co , 1950, Pg 522.
18a. Cosgriff, S. W ; Diefenbach, A. F., and Vogt, W.: Hypercoagulability of the blood associated with ACTH and cortisone therapy. *Am. J Med*, *9*.752-756, 1950.
19. Creditor, M. C , Bevans, M , Mundy, W. L., and Ragan, C.: Effect of ACTH on wound healing in humans. *Proc. Soc Exper. Biol. & Med*, *74*.245-247, 1950.
20. Crooke, A. C : Change in basophil cells of pituitary gland common to conditions which exhibit syndrome attributed to basophil adenoma *J Path. & Bact*, *41*.339-349, 1935.
21. D'Arcy Hart, P. and Rees, R J. W.. Enhancing effect of cortisone on tuberculosis in mouse. *Lancet*, *2*·391-395, 1950.
21a Dorfman, Albert, Apter, N. S , Smull, Katharine; Bergenstal, D. M., and Richter, R B Status epilepticus coincident with use of pituitary adrenocorticotropic hormone, report of three cases *J.A M.A.*, *146*·25-27, 1951.
22. Editorial Cortisone and ACTH in tuberculosis. *Lancet*, *2*. 632-633, 1950.
23. Farnsworth, E. B.: Acute and subacute glomerulonephritis

modified by adrenocorticotropin. *Proc. Soc. Exper. Biol. & Med.*, *74*:57-59, 1950.

24. Finland, M.; Kass, E. H.; and Ingbar, S. H.: Effects of ACTH in primary atypical pneumonia and in pneumococcal pneumonia. *Proc. First Clinical ACTH Conference*, edited by J R Mote, Philadelphia, The Blakiston Co., 1950, Pg. 529.
25. Forsham, P. H.; Thorn, G. W.; and Browne, J. S L.: Cited by: Cleghorn, R. A.; Graham, F. B ; Saffran, M.; and Cameron, D. E.: A study of the effect of the pituitary ACTH in depressed patients. *Canad. M. A J.*, *63*.329-331, 1950.
26. Forsham, P. H.; Thorn, G. W.; Frawley, T. F.; and Wilson, L. W.: Studies on the functional state of the adrenal cortex [illegible]
27. Fo [illegible] observations on poliomyelitis in pregnancy. *Am. J. M. Sc.*, *214*:148-152, 1947.
28. Freeman, S.; Ferling, J.; Wang, C. C.; and Smith L C.: The effect of ACTH on patients with pulmonary tuberculosis. *Proc. First Clinical ACTH Conference*, edited by J. R. Mote, Philadelphia, The Blakiston Co , 1950, Pg. 509.
29. Germuth, F. G., Nedzel, G A., Ottinger, B ; and Oyama, J.: Anatomic and histologic changes in rabbits with experimental hypersensitivity with compound E and ACTH. *Proc. Soc. Exper. Biol. & Med*, *76*.177, 1950.
30. Germuth, F. G., Jr and Ottinger, B.· Effect of 17-hydroxy-11-dehydrocorticosterone (compound E) and of ACTH on arthus reaction and antibody formation in the rabbit *Proc Soc. Exper. Biol & Med*, *74*:815-823, 1950.
31. Golden, A Bondy, P. K , and Sheldon, W. H.· Pituitary basophile hyperplasia and Crooke's hyaline changes in man after ACTH therapy *Proc. Soc Exper. Biol & Med.*, *74*· 455-458, 1950.
32. Green, H. N Suggested mode of action of corticotrophin in rheumatoid arthritis and the allergic state. *Brit M. J*, *1*.1165-1166, 1950.
33. Habif, D. V , Hare, C. C , and Glaser, G H.· Perforated duodenal ulcer associated with pituitary adrenocorticotropic hormone (ACTH) therapy. *J A.M A.*, *144*:996, 1950.
34. Hanlon, C. R . Discussion of Howes, E. L. et al (41).
35. Hardy, J D.; Riegel, C., and Erisman, E. P., Experience with

protein bound iodine (PBI); the effect of ACTH and cortisone on thyroid function *Am. J. M. Sc.*, *220*:290-292, 1950.

36. Heinbecker, P. and Pfeiffenberger, M., Jr.: Further clinical and experimental studies on the pathogenesis of Cushing's syndrome. *Am. J. Med.*, *9*:3-23, 1950.

36a. Heller, B. I.; Jacobson, W. E.; and Hammarsten, J. F.: The effect of cortisone in glomerulonephritis and the nephropathy of disseminated lupus erythematosus. *J. Lab. & Clin Med.*, *37*:133-142, 1951.

37. Hench, P. S., Kendall, E. C., Slocumb, C. H.; and Polley, H. F.: Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions. *Arch. Int. Med.*, *85*.545-666, 1950.

38. Hill, S. R., Jr; Forsham, P. H., Roche, M; and Thorn, G. W.: The response of the adrenal cortex and thyroid gland to ACTH and cortisone on patients with hyperthyroidism and the nephrotic syndrome *J Clin. Endocrinol*, *10*:823, 1950

39. Hoefer, P. F. A. and Glaser, G. H.: Effects of pituitary adrenocorticotrophic hormone (ACTH) therapy; electroencephalographic and neuropsychiatric changes in fifteen patients. *J.A.M.A.*, *143* 620-624, 1950.

40. Houssay, B A., Biasotti, A., and Rietti, C. T.. Action diabetogene de l'extrait ante-hypophysaire *Compt. rend. Soc. de biol.*, *111* 479-481, 1932.

41. Howes, E. L., Plotz, C. M, Blunt, J W.; and Ragan, C.: Retardation of wound healing by cortisone. *Surgery*, *22*. 177-181, 1950.

42 Ingle, D. J The biologic properties of cortisone· a review. *J Clin. Endocrinol*, *10* 1312-1354, 1950.

43. Ingle, D J, Higgens, G. M; and Kendall, E C · Atrophy of adrenal cortex in rat produced by administration of large amounts of cortin *Anat. Rec*, *71* 363-372, 1938

44 Irons, E. N., Ayer, J. P, Brown, R. G, and Armstrong, S. H. ACTH and cortisone in diffuse collagen disease and chronic dermatoses *J A M.A*, *145* 861-869, 1951

45. Jailer, J. W. and Knowlton, A I. Simulated adrenocortical activity during pregnancy in an Addisonian patient *J. Clin Investigation*, *29*·1430-1436, 1950.

45a. Karnofsky, D A, Stock, C C., and Rhoads, C P. The effect of adrenal steroids on growth of chick embryo *Federation Proc.*, *9*·290, 1950.

46. Kass, E. H and Finland, M.· Effect of ACTH on induced fever. *New England J. Med*, *243*.693-695, *1950*.

46a. Kilbourne, E. D. and Horsfall, F L.: Increased virus in eggs injected with cortisone. *Proc. Soc. Exper. Biol & Med*, *76*-116-118, 1951.

46b Kligman, A, M.; Baldridge G. D ; Rebell, G.; and Pillsbury, D. M.: The effect of cortisone on the pathologic responses of guinea pigs infected cutaneously with fungi viruses and bacteria. *J. Lab. & Clin. Med*, *37*.615-620, 1951.

47. Knowlton, A. I.; Loeb, E. N.; Stoerck, H C.; and Segal, B C · The development of hypertension and nephritis in normal and adrenalectomized rats treated with cortisone. *Proc. Soc. Exper. Biol. & Med*, *72*.722-725, 1949.

48. Know, A. W.: Influence of pregnancy in mice on the course of infection with murine poliomyelitis virus *Proc Soc. Exper. Biol. & Med.*, *73*:520-523, 1950

49. Kobernick, S. D. and More, R. H.: Diabetic state with lipaemia and hydropic changes in the pancreas produced in rabbits by cortisone. *Proc. Soc. Exper. Biol & Med*, *74* 602-605, 1950.

50. Kuzell, W C. and Schaffarzick, R W · Cortisone acetate in thirty-two cases; preliminary clinical observations. *Stanford Med. Bull*, *8*·125, 1950.

50a. Landauer, Walter. Potentiating effects of adrenal cortical extract on insulin abnormalities of chick development. *Endocrinology*, *41*:489-493, 1947

51. Lazarow, A. Glutathione potentiation of cortisoneinduced glycosuria in the rat. *Proc. Soc Exper Biol & Med*, *74* 702-705, 1950

51a Loosli, C. G., Hull, R B ; Berlin, B. S.; and Alexander, E. R The influence of ACTH on the course of experimental influenza type A virus infection *J Lab. & Clin Med*, *37*:464-476, 1951.

52. Lowell. F. C., Franklin, W , Beale, H. D , and Schiller, L W ·

53. M

New England M Cen., *12* 187-198, 1950

54. McDermott, W V.; Frey, E G ; Brobeck, J. R ; and Long, C N H · Mechanism of control of adrenocorticotrophic hormone. *Yale J Biol. & Med*, *23* 52-66, 1950.

55. Margolis, H. M. and Caplan, P. S.: Effects of pituitary adrenocorticotrophic hormone (ACTH) in rheumatoid arthritis. *J.A.M.A.*, *145*:382-389, 1951.
56. Massel, B. F.: Salicylates, hormones and penicillin in the treatment of rheumatic fever. *M. Clin. North America*, *34*:1419-1434, 1950.
56a. Menkin, Valy: Effect of cortisone acetate suspension on capillary permeability. *Am. J. Physiol.*, *163*:294-300, 1951.
57. Michael, Max, Jr., Cummings, M. M. and Bloom, W.L.: Course of experimental tuberculosis in the albino rat as influenced by cortisone. *Proc. Soc. Exper. Biol. & Med.*, *75*:613-616, 1950.
58. Millikan, C. H. and Eaton, L. M.: Cortisone in neurologic diseases *Proc. Staff Meet., Mayo Clin*, *25*:499-500, 1950.
58a. Morris, C. J. O R. · The adrenocorticotrophic hormone (ACTH) of the pituitary gland. *Lancet*, *1*·161-163, 1951.
59. Nelson, D. H.; Reich, H.; and Samuels, L. T.: The effect of ACTH upon the level of 17-hydroxycorticosterone in the adrenal vein blood of dogs. *J Clin Endocrinol.*, *10*.810, 1950.
60 O'Donnell, W. M. and Fajans, S. S . The adrenal cortex following ACTH: a preliminary report. *Univ. of Michigan M. Bull*, *16*·169-172, 1950.
61. Payne, T. P. B. and Duff, G L.: Serum lipids and their fractionation in alloxan diabetes in the rabbit. *Proc. Soc Exper. Biol. & Med.*, *73*.332-337, 1950.
62. Perera, G. A., Fleming, T C.; Pines, K L , and Crymble, M.: Cortisone in hypertensive vascular disease *J. Clin. Investigation*, *29* 739-744, 1950
63. Pompen, A W. M. Clinical experiences with adrenocorticotrophic hormone (corticophin) in a patient with chronic rheumatoid arthritis and in a patient with Sheehan's syndrome. *J. Clin. Ednocrinol.*, *10* 794-795, 1950.
64. Proctor, E L. and Rawson, A. J. · Adrenal cortical failure following treatment with cortisone and ACTH. *Am. J. Clin. Path.*, *21*:158, 1951
65. Queries and Minor Notes · Cortisone, mild diabetes and cardiac infarctions. *J A M.A.*, *145*:943, 1951
66. Ragan, C., Grokoest, A. W., and Boots, R. H.: Effect of adrenocorticotrophic hormone on rheumatoid arthritis. *Am. J. Med.*, *7*.741-750, 1949.
67. Recant, Lillian, Hume, D. M.; Forsham, P. H.; and Thorn, G. W.: Studies on the effect of epinephrine on the pituitary-

adrenocortical system *J. Clin. Endocrinol.*, *10*:187-229, 1950.

68. Recant, Lillian, Ott, W. H.; and Fischel, E. E.: The antipyretic effect of cortisone. *Proc. Soc. Exper. Biol. & Med*, *75*.264-266, 1950.
69. Reiner, M.: Effect of cortisone and adrenocorticotrophin therapy on serum proteins in disseminated lupus erythematosus. *Proc. Soc. Exper. Biol. & Med*, *74*:529-531, 1950.
70. Rich, A. R.; Cochran, T. H.; and McGoon, D C.: Marked lipemia resulting from the administration of cortisone. *Bull. Johns Hopkins Hosp.*, *88*:101, 1950.

70a. Riley, C. M.: Nephrotic syndrome; effect of adrenocorticotrophic hormone. *Pediatrics*, *7* 457-471, 1951.

71. Rome, H. P. and Braceland, F. J : Use of cortisone and ACTH in certain diseases, psychiatric aspects. *Proc Staff Meet*, *Mayo Clin.*, *25*.495-497, 1950.

71a. Rosenberg, E. F.: Cortisone, ACTH and other steroids in rheumatoid arthritis. *M. Clin. North America*, *35*:3-22, 1951.

71b. Sacks, M. S : Editorial: Ion exchange resins. *Ann. Int. Med.*, *34*.1066-1073, 1951.

72. Sayers, G. and Sayers, M. A.. Pituitary-adrenal system. *Recent Progr. Hormone Research*, *2*.81-115, 1948

72a Sharnoff, J. G.; Carideo, H. L ; and Stein, I D. Cortisone-treated scleroderma; report of a case with autopsy findings. *J.A.M.A*, *145*:1230-1232, 1951.

73. Selye, Hans: *The Physiology and Pathology of Exposure to Stress*, Montreal, Acta, Inc., 1950.
74. Selye, Ha
of the A
Oxford

74a. Shick, R. M.; Baggenstoss, A. H., and Polley, H. F.. Effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis. *Proc. Staff Meet.*, *Mayo Clin.*, *25*.135, 1950

75. Sh

75a. Smadel, J E.; Ley, H L.; and Diercks, F. H.: Treatment of typhoid fever. I Combined therapy with cortisone and chloramphenicol *Ann Int. Med.*, *34*·1-9, 1951.

76. Smith, R. W.; Margulis, R. R.; Brennan, M. J ; and Monto, R. W.: The influence of ACTH and cortisone on certain factors of blood coagulation. *Science*, *112* 295-297, 1950.

77. Smyth, G. A.: Activation of peptic ulcer during pituitary adrenocorticotrophic hormone therapy. *J.A.M.A.*, 145:474-477, 1951.
78. Soffer, L. J.; Gabrilove, J L.; and Jailer, J. W.: Metabolic studies with adrenocorticotrophin in Cushing's syndrome and virilism. *J. Clin. Endocrinol.*, *10*:594-602, 1950.
79. Soffer, L. J.; Levitt, M. F.; and Baehr, G ; Use of cortisone and adrenocorticotrophic hormone in acute disseminated lupus erythematosus. *Arch. Int. Med.*, *86*:558-573, 1950.
80. Somerville, W . The effect of cortisone on the cardiogram in chronic adrenal insufficiency. *Brit. M. J*, *2*:860-862, 1950.
81 Sonenberg, M ; Keston, A. S., and Money, W. L.: Tracer studies with labelled preparations of anterior pituitary hormones, ACTH. *J. Clin Endocrinol*, *10*.809, 1950.
82. Spain, D. M and Molomut, N.· Effects of cortisone on the development of tuberculous lesions in guinea pigs and on their modifications by streptomycin therapy. *Am. Rev. Tuberc.*, *62*.337-344, 1950.
83. Spiro, H. M., Reifenstein, R. W. and Gray, S. J.: The effect of adrenocorticotrophic hormone upon uropepsin excretion. *J. Lab. & Clin. Med.*, *35*·899-910, 1950.
84. Sprague, R. G., Power, M. H.; and Mason, H. L.· Physiological effects of cortisone and pituitary adrenocorticotrophic hormone (ACTH) in man. *J.A.M.A.*, *144*:1341-1347, 1950.
85. Sprague, R G. *et al.* Observations on the physiologic effects of cortisone and ACTH in man. *Arch Int. Med.*, *85*·199-258, 1950
86. Stefanini, M. and Rosenthal, M. C : Hemorrhagic diathesis with ascorbic acid during administration of anterior pituitary corticotropic hormone (ACTH) *Proc. Soc. Exper. Biol. & Med.*, *75* 806, 1950.
87. Stickney, J M , Heck, F J., and Watkins, C. H.· Cortisone and ACTH in the managment of leukemia and lymphoblastoma. *Proc. Staff Meet., Mayo Clin.*, *25*:488-489, 1950.
88 Stinchfield, F. E.: Experimental and clinical use of oxidized cellulose and cortisone in the prevention of excess bone and fibrous-tissue formation. *J Bone & Joint Surg.*, *32-A*.739-750, 1950.
89. Taylor, S. G. III; Ayer, J. P · and Morris, R. S , Jr · Cortical steroids in treatment of cancer; observations on effects of pituitary adrenocorticotropic hormone (ACTH) and cortisone

in far advanced cases. *J.A.M.A.*, *144*:1058-1064, 1950.

90. Thomas, L. and Mogabgab, W. J.· Hemorrhagic skin lesions produced by intradermal meningococcus toxin in rabbits following treatment with ACTH or cortisone. *Proc. Soc. Ecper. Biol. & Med*, *74*·829-832, 1950

91 Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R., Jr ; Roche, M.; Staehelin, D.; and Wilson, D. L : The clinical usefulness of ACTH and cortisone. *New England J. Med.*, *242*.783-793, 1950.

92 U.S. Vet. Adm. Quart. Prog Rep. (Oct.) 1950, Pg 23

93. Venning, E. H · Adrenal function in pregnancy *Endocrinology*, *39*:203-220, 1946.

94. Videbaek, A.; Asboe-Hansen, G., Astrup, P.; Faber, V.; Hamburger, C.; Schmith, K.; Sprechler, M., and Brochner-Mortensen, K.. Effect of ACTH and cortisone on rheumatic fever *Acta endocrinol*, *4*.245-264, 1950.

95 Winter, C. A ; Silber, R H.; and Stoerk, H C · Production of reversible hyperadrenocortinism in rats by prolonged administration of cortisone *Endocrinology*, *47*.60-72, 1950

96. Yoffey, J. M.; Metcalf, W. J., Herdan, G., and Nairn, V.: Effect of ACTH and suprarenal extract on bone marrow. *Brit M. J.* *1*.660-665, 1951.

77. Smyth, G. A: Activation of peptic ulcer during pituitary adrenocorticotrophic hormone therapy. *J.A.M.A.*, 145:474-477, 1951.
78. Soffer, L. J.; Gabrilove, J. L.; and Jailer, J. W.: Metabolic studies with adrenocorticotrophin in Cushing's syndrome and virilism. *J. Clin Endocrinol*, *10*:594-602, 1950.
79. Soffer, L. J., Levitt, M. F.; and Baehr, G.; Use of cortisone and adrenocorticotrophic hormone in acute disseminated lupus erythematosus *Arch. Int. Med*, *86*.558-573, 1950.
80 Somerville, W.. The effect of cortisone on the cardiogram in chronic adrenal insufficiency. *Brit. M. J.*, *2*:860-862, 1950.
81. Sonenberg, M.; Keston, A. S.; and Money, W. L.: Tracer studies with labelled preparations of anterior pituitary hormones; ACTH *J. Clin. Endocrinol.*, *10*:809, 1950.
82. Spain, D. M. and Molomut, N.: Effects of cortisone on the development of tuberculous lesions in guinea pigs and on their modifications by streptomycin therapy. *Am. Rev. Tuberc.*, *62*:337-344, 1950.
83. Spiro, H. M, Reifenstein, R. W. and Gray, S. J.· The effect of adrenocorticotrophic hormone upon uropepsin excretion. *J. Lab. & Clin Med.*, *35*·899-910, 1950.
84. [illegible]

85. Sprague, R. G. *et al*. Observations on the physiologic effects of cortisone and ACTH in man. *Arch. Int. Med*, *85*·199-258, 1950.
86 Stefanini, M. and Rosenthal, M. C.: Hemorrhagic diathesis with ascorbic acid during administration of anterior pituitary corticotropic hormone (ACTH) *Proc. Soc Exper. Biol. & Med*, *75*:806, 1950.
87. Stickney, J. M.; Heck, F. J., and Watkins, C H.. Cortisone and ACTH in the managment of leukemia and lymphoblastoma. *Proc. Staff Meet, Mayo Clin*, *25*·488-489, 1950
88. Stinchfield, F. E.: Experimental and clinical use of oxidized cellulose and cortisone in the prevention of excess bone and fibrous-tissue formation *J Bone & Joint Surg*, *32-A*:739-750, 1950.
89. Taylor, S. G. III, Ayer, J. P.: and Morris, R. S, Jr.: Cortical steroids in treatment of cancer; observations on effects of pituitary adrenocorticotropic hormone (ACTH) and cortisone

in far advanced cases. *J.A.M.A.*, *144*:1058-1064, 1950.

90 Th [illegible]

91. Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R , Jr., Roche, M.; Staehelin, D.; and Wilson, D. L.: The clinical usefulness of ACTH and cortisone. *New England J Med*, *242*:783-793, 1950.
92. U S. Vet. Adm Quart. Prog. Rep. (Oct.) 1950, Pg 23
93. Venning, E. H.: Adrenal function in pregnancy. *Endocrinology*, *39*·203-220, 1946.
94. Videbaek, A.; Asboe-Hansen, G.; Astrup, P ; Faber, V., Hamburger, C.; Schmith, K.; Sprechler, M ; and Brochner-Mortensen, K.: Effect of ACTH and cortisone on rheumatic fever. *Acta. endocrinol*, *4*·245-264, 1950.
95. Winter, C. A.; Silber, R H.; and Stoerk, H. C.: Production of [illegible]
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96. Yo [illegible]
of ACTH and suprarenal extract on bone marrow *Brit. M. J.* *1*.660-665, 1951.